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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/821,832	03/30/2001	Thomas Tuschl	0399.2008-002	6240

23628 7590 04/11/2006

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EXAMINER	
WOLLENBERGER, LOUIS V	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 04/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/821,832	TUSCHL ET AL.	
	Examiner	Art Unit	
	Louis V. Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 May 1020*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,12,16,42,43,72,74-78,81,82,84-88,91,92,94,95,106,108 and 110-114* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/11/05; 3/10/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet*.

DETAILED ACTION

Location of the Application

The location of the application has changed. The application is now located in Art Unit 1635 and has been docketed to Examiner Louis V. Wollenberger.

Response to Election

Applicants' timely election, with traverse, of cellular mRNA, in the reply filed on October 20, 2005, is acknowledged.

The traversal is on the ground(s) that it would not be unduly burdensome to search the entire claim—reciting both cellular and viral mRNA—together.

Applicants' arguments have been fully considered but are not found persuasive. MPEP §803 states that "If the search and examination of all the claims in an application can be made without serious burden, the examiner must examine them on the merits, even though they include claims to independent or distinct inventions."

In the instant case a serious burden exists since each limitation, directed to RNAs targeting either mammalian cellular or viral mRNA, requires a separate, divergent, and non co-extensive search and examination of the patent and non-patent literature. For instance, a search and consideration of the prior art as it relates to isolated RNAs targeting mammalian cellular mRNA would not be adequate to uncover prior art related to RNAs and DNA constructs encoding RNAs targeting viral mRNA.

Further, a search and examination of all the claims directed to both embodiments involves different considerations of novelty, obviousness, written description, and enablement for each claim. In view of these requirements, it is the Examiner's position that searching and

examining all of the claims including limitations to both cellular and viral mRNA in the same application presents a serious burden on the Examiner for the reasons given above and in the previous Restriction Requirement.

The requirement is still deemed proper and is therefore made FINAL.

Status of Application/Amendment/Claims

Applicant's response filed July 11, 2005, to the Final Office Action mailed on January 7, 2005, has been considered. Rejections and/or objections not reiterated from the previous office action mailed 9/1/2005 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on July 11, 2005, claims 1–3, 12, 16, 42, 43, 72, 74–78, 81, 82, 84–88, 91, 92, 94, 95, 106, 108, and 110–114 are pending and under examination.

It is also noted that Applicants use non-standard language to identify the status of the claims. For example, claims 4-11 are identified as "Canceled Herewith." Acceptable identifiers are listed in 37 CFR §1.121(c). Applicants are advised to review the status identifiers in the current claim set for compliance with 37 CFR §1.121.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is

eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submissions filed on July 11, 2005, have been entered.

Double Patenting

The list of potentially conflicting applications in this case is considered to be extensive. A sampling of such cases follows. This list may not be exhaustive.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1–3, 12, 16, 42, 43, 72, 74–78, 81, 82, 84–88, 91, 92, 94, 95, 106, and 108 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4, 7, 8, 13, 14, 20, 25, 27 of copending Application No. 10/255,568. Although the conflicting claims are not identical, they are not patentably distinct from each other

because the conflicting application claims isolated RNA of from about 21 to about 23 nucleotides that mediates RNA interference of an mRNA to which it corresponds.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims

***

Claims 1–3, 12, 16, 42, 43, 72, 74–78, 81, 82, 84–88, 91, 92, 94, 95, 106, and 108 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3, 4, 7, 8, 11, 12, 13, 14, 27, and 28 of copending Application No. 11/142,866. Although the conflicting claims are not identical, they are not patentably distinct from each other because the conflicting application claims isolated RNA of from about 21 to about 23 nucleotides that mediates RNA interference of an mRNA to which it corresponds.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims

***

Claim Objections

Claims 1–3, 12, 16, 42, 43, 72, 74–78, 81, 82, 84–88, 91, 92, 94, 95, 106, 108, and 110–114 are objected to as being drawn to a non-elected invention: RNA targeting viral mRNA.

Claims 72, 74, 75, 84, and 92 are objected to for grammatical issues that may or may not be intended. The claims are objected to, because the errors may be simply typographical and

unintentional. However, it is noted that the lack of agreement does create confusion with regard to the interpretation of the claim.

For instance, claim 72 recites "RNA segments...that have.... and mediates." Does "mediates" refer to the singular subject "Isolated DNA" or is it simply a typographical error and is really intended to refer to the plural subject "RNA segments"? If the the latter, the singular form of the verb does not agree with the plural subject.

Similar issues are present in claims 74, 75, and 84.

Claim 92 recites "RNA...that has...correspond." The form of the verb "correspond" does not agree with the subject,"RNA."

Applicant is encouraged to review the instant claims as well as all other claims for these issues.

Claims 3, 78, and 88 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

In the instant claims, the claims recite isolated RNA or isolated double-stranded RNA, which "is chemically synthesized." Absent evidence to the contrary, the recitation "chemically synthesized" is not considered to further limit the invention. How is chemically synthesized RNA any different, structurally and/or functionally, from enzymatically synthesized RNA? Is a 21-nt, unmodified siRNA synthesized by in vitro transctription any different from the same 21-nt siRNA synthesized by solid phase synthesis? If so, how? The specification does not teach any specific structural or functional differences or features of chemically synthesized RNA such that

one of skill in the art would recognize what does or does not constitute a "chemically synthesized" RNA.

Correction and/or clarification is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12, 91, 110, and 112 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 12 recites the limitation "the mRNA" in step b. There is insufficient antecedent basis for this limitation in the claim.

Claims 110 and 112 recite an isolated RNA "wherein one or more of the nucleotides of the isolated RNA are a non-naturally occurring nucleotide or deoxyribonucleotide or non-standard nucleotide." The phrase "one or more" has no upper limit. Thus, it is unclear how an RNA may be an RNA if each of the nucleotide units is a deoxyribonucleotide. Such a molecule is no longer RNA, but DNA.

In fact, the instant application provides no guidance teaching one of skill in the art how to identify a molecule as an RNA, when that molecule may be partially or even fully modified with deoxy- or non-standard nucleotides. For instance, if each of the 2'-OHs in a 21-mer is replaced with an H or F, is that molecule still considered to be an RNA? How would one of skill in the art

know whether a particular nucleic acid, fully modified with 2'-H or 2'-F, for example, is an RNA or not? It is unclear.

"RNA," as used in the instant claims, is considered to be an art-recognized term denoting polynucleotides comprising ribonucleotides having a backbone in which the 2' position of the sugar is occupied by an OH group. Yet, new claims 110 and 112, drawn to isolated RNA, encompass fully modified nucleic acids, which, technically, no longer represent RNA, but a modified derivative of RNA. Thus, claims 110 and 112 encompass DNA as well as DNA/RNA chimeras. It is, therefore, unclear how an RNA can be a DNA, and vice verse, at the same time.

Additionally, it is unclear what is meant by the term "non-standard nucleotide." The term is not defined by the claim and the specification does not provide a clear definition of the term. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the scope of the instant claims, because the metes and bounds of the term "non-standard nucleotide" cannot be ascertained.

Claim 91 is rejected as indefinite because the claim recites a composition but specifies only one component in the composition. For instance, the claim does not specify a carrier or any other component needed to complete the composition.

Appropriate corrections are required.

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The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Claim 113 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 113, added by amendment on July 11, 2005, recites an isolated RNA of about 21 to about 24 nucleotides in length. Clear support for the new limitation "of about 24 nucleotides in length" cannot be found in the instant application or priority documents. Accordingly, claim 113 is considered to constitute new matter.

Curiously, while, on the one hand, rejecting the notion that Fire et al. anticipates claims to RNAs of about 21 to about 23 nucleotides in length because Fire et al. discloses dsRNAs of at least 25 nucleotides in length, Applicants argue, on the other, that support for new claim 113 can be found within the original limitation of "about 23," stating that "about 23" clearly encompasses an upper limit of 24 (page 9 of Applicants' remarks). How Applicants have determined that "about 23" has an upper limit of exactly 24 is unclear. Furthermore, no teaching in the instant application can be found clearly informing one of skill in the art that the term "about 23" has an upper limit, much less that the upper limit is exactly 24 but definitely not 25. In fact the quantitative value and range of the recitation "about 23" remains unclear, and the use of the term "about" in the instant claims is considered to impart significant breadth to the claims.

Accordingly, Claim 113 is rejected for lack of clear written description support. If applicants believe that support for claim 113, drawn to RNAs of 24 nucleotides in length, is

present in the instant application or earlier filed priority documents, applicant must, in responding to this Office Action, point out with particularity, where such support may be found.

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Claims 43, 81, and 91 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in a determination of lack of enablement include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

The claims are drawn to pharmaceutical compositions comprising RNA that mediates RNA interference by directing cleavage of the mRNA to which it corresponds. The "pharmaceutical composition" language in combination with the fact that the specification (page

7) discloses using the RNA-containing pharmaceutical compositions for treating disease in individuals comprising administering the RNA to an individual, specifically a human (page 17), requires that these claims be evaluated to determine whether the specification teaches how to use these compositions for treating these conditions.

Problems related to the pharmaceutical use of nucleic acids in general, and antisense and siRNA nucleic acids in particular, are evident from the post filing art.

For instance, the post-filing art indicates that the art of *in vivo* delivery of dsRNAs and other nucleic acids into targeted cells, tissues, and organs was highly unpredictable.

Such problems include the inability to routinely deliver an effective concentration of a specific nucleic acid in a target cell, such that a target gene is inhibited to a degree necessary to produce a therapeutic effect.

Gerwirtz et al. (1998) *Blood* 92(3):712-736, for example, teach that

> "...delivery of oligonucleotides remains an important problem..." (page 728). "The ability to deliver ODN into cells and have them reach their target in a bioavailable form must be further investigated. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient." (page 728)

Jen et al. (2000) *Stem Cells* 18:307-319 teach that

> "One of the major limitations for the therapeutic use of AS-ODNS and ribozymes is the problem of delivery....presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable". Jen et al. outlines many of the factors limiting the application of antisense for therapeutic purposes and concludes (see p 315, second column), "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive." (page 313, second column, second paragraph):

Lu et al. (2005) in *RNA Interference Technology* (Cambridge, Appasani, ed.), page 303, state that "Unlike *in vitro* transfection of siRNA into cells, *in vivo* delivery of siRNA into targeted tissue in animal models is much more complicated, involving physical, chemical and

biological approaches, and in some cases their combination." Therapeutic applications, however, clearly depend upon optimized local and systemic delivery of siRNA *in vivo*. "....limited reports of *in vivo* studies have indicated a lack of effective delivery methods for siRNA agents." "...the two most critical hurdles are maintaining its [siRNA] stability *in vivo* and delivery to disease tissues and cells." (page 314) Lu et al. admit that while hydrodynamic delivery of siRNA duplexes into mouse liver has proven to be quite efficient, this technique is not clinically feasible in human studies.

Samarsky et al. in *RNA Interference Technology,* pages 389-394, appear to agree with Lu et al., stating that "Delivery of RNAi to target cells and tissues in mammalian organism[s] is considerably more difficult than in cultured cells. This step is likely to be a critical bottleneck in the *in vivo* application of RNAi." "One major remaining obstacle is the efficient delivery of RNAi triggers to target tissues *in vivo*." (page 394).

Sioud in *RNA Silencing, Methods and Protocols,* (Humana Press, 2005) expresses similar reservations, specifically with respect to the use of cationic carriers, as currently claimed in claims 34 and 35. On page 238, Sioud states "Despite some encouraging results, however, liposomes still have not the characteristics to be perfect carriers because of toxixity, short circulation time, and limited intracellular delivery for target cells." And on page 243, "The in vivo uptake of siRNAs can differ dramatically with cell types as well as with the status of cell differentiation." "...certain synthetic siRNAs activated the production of TNF-α and interleukin (IL)-6 in human freshly isolated monocytes..."

Similarly, Simeoni et al. also in *RNA Silencing, Methods and Protocols,* state on page 251 "So far, although siRNA transfection can be achieved with classical laboratory-cultured cell lines using lipid-based formulations, siRNA delivery remains a major challenge for many cell lines and there is still no reasonably efficient method for in vivo application."

In view of the express teachings of the post-filing art suggesting that in vivo delivery of siRNA is unpredictable, it is essential that the instant application provide enabling disclosure showing how to use the pharmaceutical compositions of the instant invention to target any desired gene in any cell in any animal.

A review of the instant application fails to find adequate representations or guidance exemplifying the *in vivo* applications currently contemplated for which the pharmaceutical compositions are intended. A review of the instant application finds 5 working examples, all of which are directed to methods for reducing gene expression in cultured cells, using siRNA. No technical guidance or exemplary disclosure is provided regarding the use of the claimed methods for targeting genes in living organisms, including any mammal. As the post-filing art indicates, in culture results are not readily extrapolated to *in vivo* applications.

Thus, the amount of disclosure is insufficient to support the instant claims to "pharmaceutical compositions" given the level of unpredictability in the art. For example, the instant application does not appear to teach one of skill in the art how to effectively target tissues and cells in the brain. Similarly, while the instant application is enabling for the use of RNA *in vitro* in cultured cells, it does not enable the use of these RNAs *in vivo* in mammals, including humans.

Thus, considering the breadth of the claims, the state of the art at the time of filing, the level of unpredictability in the art, and the limited guidance and working examples provided by the instant application, the Examiner submits that the skilled artisan would be required to conduct undue, trial and error experimentation to use the claimed invention commensurate with the claims scope.

Accordingly, the instant claims are rejected for failing to comply with the enablement requirement. Removing the "pharmaceutical" language from the instant claims would overcome this rejection.

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Claims 110–112 and 114 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims are drawn to isolated RNA of from about 21 to about 23 nucleotides that mediates RNA interference of a corresponding mRNA, wherein the mRNA is mammalian mRNA, and wherein one or more nucleotides of the isolated RNA are non-naturally occurring nucleotides or deoxyribonucleotides. As explained above, "one or more" has no upper limit and includes fully modified RNAs.

Thus, the instant claims encompass DNA and, apparently, DNA/DNA duplexes, for mediating RNA interference. The claims also encompass fully modified RNA and RNA/RNA

duplexes, such as fully 2'-O-methyl modified siRNAs. The claims, in fact, encompass any modification, such as any non-standard nucleotide.

A review of the instant application fails to find any examples, working or prophetic, demonstrating or teaching the used of partially and/or fully modified RNAs for RNA interference in any cell or organism. Thus, no technical guidance or exemplary disclosure is provided regarding the use of such modified RNAs for targeting genes in living organisms, including any mammal.

The post-filing art and related literature is replete with reports showing that fully modified RNAs, and some partially modified RNAs, for inducing RNA interference were not enabled at the time the instant application was effectively filed.

In fact Applicant's own work demonstrates that fully modified siRNA duplexes, comprising 2'-deoxy or 2'-O-methyl substituents were ineffective as mediators of RNAi in model RNAi systems.

For instance, Tuschl et al. (US 2004/0259247 A1) teach, for example, that 8 out of 42 nt of a siRNA duplex can be replaced by DNA residues without loss of activity. Complete substitution of one or both siRNA strands by 2'-deoxy residues, however, abolishes RNAi, as did substitution by 2'-O-methyl residues (paragraph 166 and Fig. 14).

With regard to partially modified dsRNAs, Amarzguioui et al. (2003) *Nucleic Acids Res.* 31:589-595 teach that 5'-end modified siRNAs function poorly or not at all. On page 591 and in Fig 3 they show that "Allylated siRNAs…showed reduced effectivity even with only one substituent in the 5' end."

A review of the instant application fails to find adequate representations exemplifying or teaching the use of the instantly claimed modified nucleic acid molecules for RNA interference.

Considering the breadth of the claims, the state of the art at the time of filing, the level of unpredictability in the art, and the limited guidance and working examples provided by the instant application, the Examiner submits that the skilled artisan would be required to conduct undue, trial and error experimentation to practice the claimed invention commensurate with the claims scope.

Accordingly, the instant claims are rejected for failing to comply with the enablement requirement.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 12 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Broadest reasonable interpretation of Claim 12 includes a product of nature. Adding the word "isolated" or "purified," for example, would overcome this rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 3, 12, 16, 86, 87, 88, 106, 108, and 110–114 are rejected under 35 U.S.C. 102(b) as being anticipated by Wu et al. (1998) *J. Biol. Chem* 273:2532–2542.

Wu et al. teach 17-nt RNA/RNA duplexes targeting human Ha-Ras mRNA for use in antisense therapeutics (Figs. 1 and 2). The duplexes are expressly taught as comprising sense and antisense oligoribonucleotides, wherein the antisense strand is designed for sequence specific inhibition of Ha-Ras gene expression (see results at Fig. 2, page 2535).

The disclosed duplexes (Fig. 2) comprise one or more modified nucleotides and/or internucleoside linkages flanking the central RNA sequence. The duplexes are said to be chemically synthesized (page 2533).

The 17-nt duplexes and antisense RNAs disclosed by Wu et al. are considered to be well within the range of "about 21 to about 23 nucleotides" in length, as now recited in the instant claims because Applicants do not define the term "about" in a way that clearly limits the claim to any particular range of RNAs.

Claims 3, 12, and 16 are drafted in the product-by-process format. Fire et al. do not describe the production of the molecule using the methods identical to that is recited in claim 12 and 16. However, the recitation of a process limitation in claims 12 and 16 is not viewed as positively limiting the claimed product absent a showing that the process of making recited in

claims 12 and 16 imparts a novel or unexpected property to the claimed product, as it is assumed that equivalent products are obtainable by multiple routes. The burden is placed upon the applicants to establish a patentable distinction between the claimed and references products. The method in which the RNAs were produced is immaterial to their patentability.

> "Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product I in the product-by-process claim I is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re* Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP 2113.
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> ***

Claims 1–3, 12, 16, 43, 72, 74–78, 81, 86–88, 91, 92, 94, 95, 106, 108, 110–114 are rejected under 35 U.S.C. 102(b) as being anticipated by Szyf et al. (US Patent 5,578,716), as evidenced by Zhang et al. (2004) *Cell* 118:57–68.

At the outset, it is noted that claims 110–112 embrace DNA oligonucleotides.

Szyf et al. teach 20-nt antisense oligonucleotides for inhibiting mammalian DNA MeTase mRNA (column 3, bottom, for example, and Example 8, column 15). The oligonucleotides are said to be complementary to mRNA or double-stranded DNA that express mammalian, and, in particular, human or mouse, DNA methyl transferase. It is taught that oligonucleotides may be in the form of a hybrid oligonucleotide having regions of deoxyribonucleotides and regions ribonucleotides or 2'-substituted ribonucleotides. And that, preferably, from about one to about all of the internucleoside linkages are phosphorothioate (columns 5-6). It is taught that the antisense oligonucleotides may be "self-stabilized," having a self-complementary region that hybridizes intramolecularly with the oligonucleotide to form an exonuclease resistant hairpin-like structure (column 6, lines 45-65). In this way, it is said, Modified oligonucleotides according

to this embodiment of the invention are generally characterized by having two regions: a DNA MeTase hybridizing region and a self-complementary region. The DNA MeTase hybridizing region has a nucleotide sequence that is complementary to an essential nucleic acid sequence of DNA MeTase. Preferably, this region has from about 6 to about 100 nucleotides. In this embodiment, the oligonucleotide is stabilized, i.e., rendered resistant to exonucleolytic degradation by base-pairing between the target hybridizing region and the self-complementary region and/or by base-pairing between complementary sequences within the self-complementary region (columns 6 and 7).

The antisense oligonucleotides may be introduced into mammalian cells via a vector construct such as that taught at column 8, Example 1. Thus, Szyf et al. also disclose an isolated DNA encoding antisense RNA. Upon binding to the target mRNA, it would be expected that the endogenous Dicer, or RNas III activity in the cell would process the antisense RNA/target mRNA duplex into segments of about 21 to about 23 nucleotides in length, as evidenced by Zhang et al. (2004) *Cell* 118:57–68, who teach that Dicer is a multidomain ribonuclease that processes long dsRNAs to fragments of 15-21 nucleotides during RNA interference.

Szyf et al. teach that the disclosed oligos may be formulated for use as therapeutic agents (column 7, bottom) and may be synthesized by solid phase methods (column 5).

Although Szyf et al. do not teach that their oligos mediate "RNA inteference," the self-stabilized, double-stranded molecules would be expected to inherently perform this function because they meet the structural limitations of the claims.

Claims 3, 12, 16, 78, and 88 are drafted in the product-by-process format. Fire et al. do not describe the production of the molecule using the methods identical to that is recited in claim

12 and 16. However, the recitation of a process limitation in claims 12 and 16 is not viewed as positively limiting the claimed product absent a showing that the process of making recited in claims 12 and 16 imparts a novel or unexpected property to the claimed product, as it is assumed that equivalent products are obtainable by multiple routes. The burden is placed upon the applicants to establish a patentable distinction between the claimed and references products. The method in which the RNAs were produced is immaterial to their patentability.

> "Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product I in the product-by-process claim I is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re* Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP 2113.

Accordingly, the instant claims are anticipated.

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Claims 1–3, 12, 16, 43, 76, 77, 78, 81, 86–88, 91, 106, 108, 110–114 are rejected under 35 U.S.C. 102(b) as being anticipated by Agrawal et al. (WO 94/01550).

Agrawal et al. teach self-stabilized, hairpin (i.e., double stranded) RNAs that form stable duplexes, resist nucleolytic degradation and activate RNase H, for inhibiting gene expression in cells and animals (pages 3, 8, 11, 12, and 19, and see Figs. 1, 5, and 6, for example.). For example, at page 5, Agrawal and Tang teach that "The advantages of oligonucleotides according to the invention, known as self-stabilized oligonucleotides, arise from the presence of two structural features: a target hybridizing region and a self-complementary region. The target hybridizing region comprises an oligonucleotide sequence complementary to a nucleic acid sequence that is from a plant or animal virus, a pathogenic organism, or a cellular gene or gene transcript, the abnormal gene expression or product of which results in a disease state. The self-

complementary region comprises an oligonucleotide sequence that is complementary to a nucleic acid sequence within the oligonucleotide. Thus, at least when the oligonucleotide is not hybridized to a target nucleic acid sequence, the oligonucleotide forms a totally or partially double stranded structure that is resistant to nucleolytic degradation. [...] This results in oligonucleotides that activate RNase H, an important feature for the antisense therapeutic compound."

Agrawal and Tang further teach that the "... target hybridizing region is from about 8 to about 50 nucleotides in length" (page 9-10); that "In a preferred embodiment, there are about 10 intramolecular base-pairs formed in the self-stabilized oligonucleotide, with the 10 base pairs being consecutive and involving the 3'-most nucleotides. Of course, the intra-molecular base-pairing can be so extensive as to involve every nucleotide of the oligonucleotide. Preferably, this will involve a self-complementary region of about 50 nucleotides or less." (page 15); and that the "...target hybridizing region of oligonucleotides according to the invention may contain ribonucleotides, deoxyribonucleotides or any analogs of ribonucleotides or deoxyribonucleotides." (page 13). On page 10, it is stated that "For purposes of the invention, the term "oligonucleotide sequence that is complementary to a nucleic acid sequence" is intended to mean an oligonucleotide sequence (2 to about 50 nucleotides) that hybridizes to the nucleic acid sequence under physiological conditions,e.a., by Watson-Crick base paring (interaction between oligonucleotide and single-stranded nucleic acid) or by Hoogsteen base pairing. (interaction between oligonucleotide and doublestranded nucleic acid) or by any other means. Such hybridization under physiological conditions is measured as a practical matter by observing interference with the function of the nucleic acid."

Agrawal et al. teach that the self-stabilized, duplex oligonucleotide includes polymers of ribonucleotides, deoxyribonucleotides, or both (pages 8 and 14). The oligonucleotides may comprise modifications such as phosphorothioates (page 5). Figs. 1 and 5 shows various embodiments of the invention, indicating the hairpin structure and showing the mechanism by which the duplexes are predicted to hybridize with target mRNA.

Accordingly, Agrawal et al. anticipates the instant claims.

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Claims 1–3, 43, 81, 86–88, 91, 106, 108, 110–114 are rejected under 35 U.S.C. 102(e) as being anticipated by Crooke (US 6,107,094).

Crooke discloses in example 27-a, at columns 50 and 51 and in Table 1, fully complementary double stranded RNAs 17 and 20 nucleotides in length targeted to either Ha-ras or C-raf, genes that have been identified in the mammalian genome (column 11, lines 39-41). It appears from the disclosure at column 50, for example, that the duplex RNAs comprise a 3'-terminal hydroxyl group either in the sense strand, the antisense strand, or both. For example, Crooke teaches that nuclease cleavage of these duplexes generates a 3'-hydroxyl (column 15, bottom).

Crooke teaches at column 14, bottom, that the oligoribonucleotides may be conveniently and routinely made using the well-known technique of solid phase synthesis—i.,e., Crooke teaches that the oligoribonucleotide duplexes may be chemically synthesized. See also Example 6, column 38.

At column 16, top, Crooke teaches that the compounds of the invention, including the oligoribonucleotides disclosed, can be utilized as diagnostics, therapeutics and as research

reagents. As such, the RNA oligos may be formulated and used as pharmaceutical compositions by adding an effective amount of the compound to a suitable pharmaceutically acceptable diluent or carrier.

Crooke further discloses that the double stranded RNAs are modified with phosphorothioates and/or 2'-methoxynucleosides and that the double stranded RNAs are nuclease resistant (columns 50-51, Example 27-a).

Although Crooke does not specifically teach that these double-stranded RNAs, and pharmaceutical compositions thereof, may be used to mediate RNA interference by directing cleavage of the mRNA to which it corresponds, this effect is considered to be an inherent property of the disclosed RNAs, since the RNAs meet all of the structural limitations of the instant claims (MPEP §2112). Because they meet these structural limitations their biological properties and activities are considered be inherently disclosed.

Moreover, Crooke clearly contemplates using the oligoribonucleotides of his invention, including those disclosed in Table 1, in therapeutic and research applications to reduce target RNA levels, principally through the action of RNase H, an endonuclease that cleaves the RNA strand of DNA:RNA duplexes (columns 1-2). See, also, columns 11 and 12, regarding the inhibition of H-ras genes in particular using the disclosed oligoribonucleotides. Accordingly, it is clear that the duplexes disclosed are intended to be used to interfere with RNA translation/expression.

Furthermore, Applicants' remarks on pages 10–14 of their reply, rebutting the previous rejection for lack of written description of the broad genus of RNAs now claimed, provide a basis for the reasonable presumption that the RNA sense/antisense duplexes disclosed by Crooke

in Table 1 would inherently behave as mediators of RNA interference. The duplexes are "about" 21 to about 23 nucleotides in length and correspond to a mammalian cellular mRNA. Applicants state "It is not necessary for Applicant to identify the cleavage site of the mRNA to which the isolated RNA corresponds. The isolated RNA has sequence correspondence to the mRNA" (page 10). "The invention is based, at least in part, on the recognition that RNA having certain particular structural features, such as a size of about 21 to about 23 nucleotides in length and sequence correspondence with a target mRNA was sufficient to induce degradation of the target mRNA by RNAi when exposed to the target mRNA/gene in a cellular system. These structural and functional properties are associated with the entire genus of claimed molecules" (page 10).

Furthermore, claims 1–4 of Applicants' priority document EPO 00 126 325.0 expressly claim double stranded RNAs of 19 and 20 nucleotides for mediating RNA interference.

Accordingly, while Crooke does not disclose that these RNAs will inhibit gene expression, Crooke meets all structural limitations of the claims. The RNAs would, therefore, absent evidence to the contrary, be expected to inhibit gene expression via RNA interference.

Thus, Crooke discloses all limitations of and anticipates claims 4 and 6-9.

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Claims 1–3, 12, 16, 42, 43, 72, 74–78, 81, 82, 84–88, 91, 92, 94, 95, 106, 108, 110–114 are rejected under 35 U.S.C. 102(e) as being anticipated by Fire et al. (US 6,506,559), as evidenced by Meister et al. (2004) *Nature* 431:343–349.

The claims are directed to double stranded RNAs that are 15-21 nucleotides in length that specifically inhibit the expression of a mammalian target gene wherein one strand is complementary to less than the full-length of a target gene.

Fire et al. disclose that double-stranded RNA causes potent and specific RNA interference and that double-stranded RNA is substantially more effective at producing interference than either strand individually. Fire et al. disclose that one strand of the RNA is complementary to the target gene. Fire et al. further disclose that this effect can be used to inhibit any target gene, including any endogenous target gene derived from any organism, including any vertebrate or invertebrate animal (columns 4 ,8, and 11 for example). Fire et al. teach that the dsRNAs of their invention may be synthesized enzymatically or by partial/total organic synthesis, and that any modified ribonucleotide can be introduced by in vitro enzymatic or organic synthesis (column 7, lines 35-40). The RNA may comprise modifications to either the sugar-phosphate backbone or the nucleoside (column 7). For example, the dsRNAs may comprise phosphodiester linkages having nitrogen or sulfur atoms (column 7, lines 30-40).

Fire et al. teach further that a general strategy for the production of dsRNAs is to clone segments of interest between flanking copies of the bacteriophage T7 promoter into a bacterial plasmid construct. The construct may then be introduced into the target cell or organism by an appropriate method (see Fig. 5, columns 6, 9, and 21).

Fire et al. teach that dsRNAs for use in gene inhibition should contain sequences identical to the target gene (column 7, lines 50-55), and describe methods for ensuring such identity as part of the design of such dsRNAs.

While the invention of Fire et al. is directed to the use of dsRNAs greater than 21–23 nucleotides in length—e.g., Fire et al. teach that dsRNAs for gene inhibition are at least 25 nucleotides or even 400 nucleotides in length (column 8)—the dsRNAs taught by Fire et al. for use in gene silencing in any animal are, nevertheless, considered to be an inherent disclosure of

the instantly claimed RNAs, 21 to 23 nucleotides in length, since the dsRNAs taught by Fire et al. are inevitably processed into dsRNAs of 21 to 23 nucleotides in length following administration to the cell, including any vertebrate cell, as evidenced by the post-filing art of Meister et al. That is, the formation of 21 to 23 nucleotide RNAs is a necessary consequence of administering long dsRNAs to cells *in vitro* and *in vivo*. The short, 21-23 nucleotide RNAs now claimed are, therefore, inherently disclosed by Fire et al., even though Fire et al. may not have recognized at the time that the disclosed dsRNAs were broken down in the cell into 21–23 nucleotide RNAs, which then act as the mediators of the gene specific silencing effect described by Fire et al. In other words, short, 21-23 nucleotide RNAs are formed naturally, in the cell, as the active metabolites of a long dsRNA, which Fire et al. teach may be introduced into a cell to inhibit the expression of gene to which it corresponds. A gene is, thereby, identified base on the sequence-specific down regulation of the gene and detection of a resulting phenotype, as compared to no effect with the negative control dsRNA.

Thus, the dsRNAs taught by Fire et al. inherently comprise 21–23 nucleotide dsRNAs, as now claimed. Moreover, as an issued patent, Fire et al. is presumed to provide an enabling disclosure for making and using dsRNAs to inhibit gene expression in animal cells (see claim 6, for example).

Thus, although Fire et al. are silent as to the cleavage of long dsRNAs into double stranded duplexes 21–23 nucleotides in length, the long dsRNA molecules disclosed by Fire et al. are necessarily cleaved into such duplexes when these duplexes are administered to animals or introduced into mammalian cells, as evidenced by Meister et al.

Meister et al. teach that, like miRNA precursores, long dsRNA is processed by the RNase III enzyme Dicer into 21–23 nucleotide dsRNA intermediates (Fig. 2, legend, page 346, for example). The processing of dsRNAs by Dicer yields RNA duplexes of about 21 nucleotides in length, which have 5' phosphates and 2-nucleotide 3' overhangs (page 343). Absent evidence to the contrary, the 21-nt products are expected to comprise terminal 3'-hydroxyl groups following hydrolysis of the phosphodiester bond, catalyzed by Dicer. Meister et al. teach further that several organisms contain more than one Dicer gene. Mammals are said to possess one Dicer gene (page 344), the action of which is schematically represented in Fig. 1, page 344.

As stated in the MPEP (see MPEP 2112), something that is old does not become patentable upon the discovery of a new property. The claiming of an unknown property, which is inherently present in the prior art, does not necessarily make the claim patentable. There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of the invention, but only that the subject matter is in fact inherent in the prior art reference.

This inherency argument is bolstered by *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67USPQ2d 1664, 1668 (Fed. Cir. 2003). Inherent anticipation does not require recognition in the prior art.

Since Fire et al. teach administering dsRNA and the resultant RNA interference, and it has since been discovered that this effect is mediated by the activity of Dicer, which cleaves long dsRNA into fragments that are ~21 nucleotides long, the teachings of Fire et al. anticipate the instant invention. Furthermore, see *Eli Lilly & Co. v. Barr Labs., Inc., 251* F.3d 955, 970, 58 USPQ2d 1865 (Fed. Cir. 2001), "a limitation or the entire invention is inherent and in the public

domain if it is the "natural result flowing from" the explicit disclosure of the prior art". This is considered to inherently anticipate the compound even though the compound's existence was not known.

Claims 3, 12, 16, 78, and 88 are drafted in the product-by-process format. Fire et al. do not describe the production of the molecule using the methods identical to that is recited in claim 12 and 16. However, the recitation of a process limitation in claims 12 and 16 is not viewed as positively limiting the claimed product absent a showing that the process of making recited in claims 12 and 16 imparts a novel or unexpected property to the claimed product, as it is assumed that equivalent products are obtainable by multiple routes. The burden is placed upon the applicants to establish a patentable distinction between the claimed and references products. The method in which the RNAs were produced is immaterial to their patentability.

> "Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product I in the product-by-process claim I is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re* Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP 2113.

Therefore, the instant claims are anticipated by Fire et al., as evidenced by Meister et al.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis V. Wollenberger whose telephone number is 571-272-8144. The examiner can normally be reached on Mon–Fri, 8:00 am–4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Art Unit 1635
March 30, 2006

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